



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07C 237/06, A61K 31/16, C07C 321/30</b>		A1	(11) International Publication Number: <b>WO 97/05102</b>
			(43) International Publication Date: 13 February 1997 (13.02.97)
(21) International Application Number: PCT/EP96/02961 (22) International Filing Date: 5 July 1996 (05.07.96) (30) Priority Data: 9515412.6                      27 July 1995 (27.07.95)                      GB (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milan (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): PEVARELLO, Paolo [IT/IT]; Piazza San Pietro in Ciel d'Oro, 7/A, I-27100 Pavia (IT). AMICI, Raffaella [IT/IT]; Via N. Rocca, 11, I-29100 Piacenza (IT). VARASI, Mario [IT/IT]; Via Giambellino, 80, I-20146 Milan (IT). BONSIGNORI, Alberto [IT/IT]; Via dei Benedettini, 2, I-20146 Milan (IT). SALVATI, Patricia [IT/IT]; Via Valesa, 16/C, I-20020 Arese (IT).		(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report.	
(54) Title: 2-(4-SUBSTITUTED)-BENZYLAMINO-2-METHYL-PROPANAMIDE DERIVATIVES  <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>			
(57) Abstract  Novel 2-(4-substituted)-benzylamino-2-methyl-propanamides compounds, having CNS activity, of general formula (I) wherein: n is zero, 1, 2 or 3; X is -O-, -S-, -CH2- or -NH-; each of R and R <sub>1</sub> independently is hydrogen, C <sub>1</sub> -C <sub>6</sub> alkyl, halogen, hydroxy, C <sub>1</sub> -C <sub>4</sub> alkoxy or trifluoromethyl; each of R <sub>2</sub> , R <sub>3</sub> and R <sub>4</sub> independently is hydrogen, C <sub>1</sub> -C <sub>6</sub> alkyl or C <sub>3</sub> -C <sub>7</sub> cycloalkyl; and the pharmaceutically acceptable salts thereof, are disclosed.			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

**2-(4-SUBSTITUTED)-BENZYLAMINO-2-METHYL-PROPANAMIDE  
DERIVATIVES**

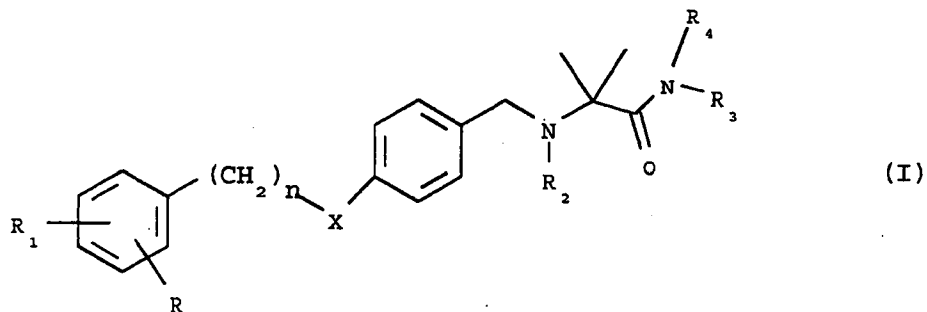
The present invention relates to novel 2-(4-substituted)-  
5 benzylamino-2-methyl-propanamides, to their use as  
therapeutic agents, to a process for their preparation and to  
pharmaceutically compositions containing them.

WO 90/14334 discloses N-phenylalkyl substituted  $\alpha$ -amino  
carboxamide derivatives active on the CNS.

10 It has been found that novel 2-(4-substituted)-benzylamino-2-  
methyl-propanamides derivatives as herein defined have  
valuable biological properties, in particular as  
antiepileptic, anti-Parkinson, neuroprotective, anti-  
depressant, antispastic and/or hypnotic agent.

15

The present invention provides novel compounds of the  
following general formula (I)



wherein:

20 n is zero, 1, 2 or 3;

X is -O-, -S-, -CH<sub>2</sub>- or -NH-;

each of R and R<sub>1</sub> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,  
halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy or trifluoromethyl;

each of R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl  
25 or C<sub>3</sub>-C<sub>7</sub> cycloalkyl;

and the pharmaceutically acceptable salts thereof.

The pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts with inorganic, e.g. hydrochloric, hydrobromic, sulfuric, and phosphoric acids, or organic, e.g. acetic, propionic, lactic, oxalic, malic, maleic, tartaric, citric, benzoic, mandelic, C<sub>1</sub>-C<sub>4</sub> alkylsulfonic, salicylic and fumaric acids.

The compounds of the formula (I), their pharmaceutically acceptable salts may also form pharmaceutically acceptable solvates, such as mono-, di- or tri-hydrates, which are also object of the present invention.

The alkyl and alkoxy groups may be branched or straight groups.

A C<sub>1</sub>-C<sub>6</sub> alkyl group is preferably a C<sub>1</sub>-C<sub>4</sub> alkyl group, in particular methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, more preferably methyl or ethyl.

Representative examples of C<sub>1</sub>-C<sub>4</sub> alkoxy groups include methoxy or ethoxy.

A halogen atom is e.g. chlorine, fluorine or bromine.

A C<sub>3</sub>-C<sub>7</sub> cycloalkyl group is, for instance, a cyclopropyl, cyclohexyl or cycloheptyl group, in particular cyclopropyl.

The present invention also include within its scope all the possible isomers of the compounds of formula (I) and their mixtures, as well as the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

Preferred compounds of the invention are the compounds of formula (I) wherein

n is 1 or 2;

X is -O-, -S- or -NH-;

R is hydrogen;

R<sub>1</sub> is hydrogen or halogen;

each of  $R_2$ ,  $R_3$  and  $R_4$  independently is hydrogen or  $C_1$ - $C_4$  alkyl; and the pharmaceutically acceptable salts thereof.

More preferred compounds of the invention are the compounds  
5 of formula (I), wherein  
n is 1;  
X is -O-, -S- or -NH-;  
 $R_1$  is hydrogen or halogen;  
 $R$ ,  $R_2$ ,  $R_3$  and  $R_4$  are hydrogen; and the pharmaceutically  
10 acceptable salts thereof.

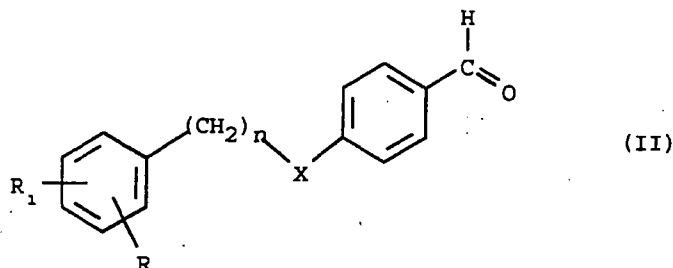
Examples of specific compounds of the invention are:

2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;  
2-[4-(3-chlorobenzyloxy)benzylamino]-2-methyl-propanamide;  
15 2-[4-(4-chlorobenzyloxy)benzylamino]-2-methyl-propanamide;  
2-[4-(3-bromobenzyloxy)benzylamino]-2-methyl-propanamide;  
2-[4-(4-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;  
2-[4-(2-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;  
2-[4-(3-fluorobenzylamino)benzylamino]-2-methyl-propanamide;  
20 2-[4-(benzylsulfanyl)benzylamino]-2-methyl-propanamide;  
2-[4-(3-fluorobenzyloxy)benzylmethylamino]-2-methyl-  
propanamide;  
2-{[4-(3-fluorobenzyloxy)benzyl]-amino}-2-methyl-N-methyl-  
propanamide;  
25 2-{[4-(3-chlorobenzyloxy)benzyl]methylamino}-2-methyl-  
propanamide; and  
2-{[4-(3-bromobenzyloxy)benzyl]methylamino}-2-methyl-  
propanamide, if the case, either as single (S) or (R) isomer  
or as a mixture thereof, and the pharmaceutically acceptable  
30 salts thereof.

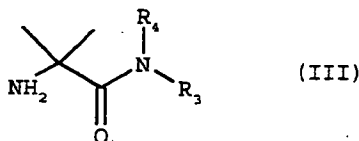
The compounds of the invention and the salts thereof can be

obtained by a process comprising:

- a) reacting a compound of formula (II)



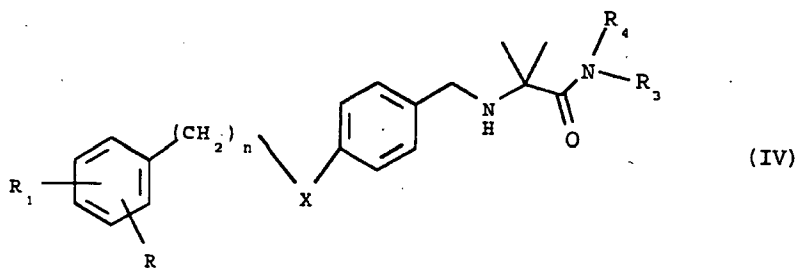
- 5 wherein n, R, R<sub>1</sub> and X are as defined above, with a compound of formula (III)



wherein R<sub>3</sub> and R<sub>4</sub> are as defined above, thus obtaining a compound of formula (I) in which R<sub>2</sub> is hydrogen; or

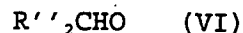
10

- b) reacting a compound of formula (IV)



wherein R, R<sub>1</sub>, R<sub>3</sub>, R<sub>4</sub>, n and X are as defined above, with a compound of formula (V) or (VI)

15



wherein W is a halogen atom; R'<sub>2</sub> is a C<sub>1</sub>-C<sub>6</sub> alkyl and R''<sub>2</sub> is hydrogen or C<sub>1</sub>-C<sub>5</sub> alkyl, thus obtaining a compound of the invention in which R<sub>2</sub> is C<sub>1</sub>-C<sub>6</sub> alkyl; and, if desired, converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a

20

pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound.

5 All the processes described hereabove are analogy processes and can be carried out according to well known methods in organic chemistry.

A compound of formula (IV) is a compound of formula (I) in which  $R_2$  is hydrogen.

10 The reaction of a compound of formula (II) with a compound of formula (III) to give a compound of formula (I) or (IV) is a reductive amination reaction which can be carried out according to well known methods. According to a preferred embodiment of the invention it may be performed under nitrogen atmosphere, in a suitable organic solvent, such as  
15 an alcohol, e.g. a lower alkanol, in particular methanol, or in acetonitrile, at a temperature ranging from about 0°C to about 40°C, in the presence of a reducing agent, the most appropriate being sodium cyanoborohydride. Occasionally molecular sieves can be added to the reaction mixture for  
20 facilitating the reaction.

In a compound of formula (V) the halogen W is preferably iodine. The alkylation reaction of a compound of formula (IV) with a compound of formula (V) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol,  
25 ethanol or isopropanol, in particular in ethanol, at a temperature ranging from about 0°C to about 50°C.

The alkylation reaction of a compound of formula (IV) with an aldehyde of formula (VI) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, ethanol  
30 or acetonitrile in the presence of a suitable reducing agent, such as sodium cyanoborohydride, at a temperature ranging from about 0°C to about 30°C.

A compound of the invention can be converted, as stated above, into another compound of the invention by known methods. Process-variant b) above may be regarded as an example of optional conversion of a compound of the invention  
5 into another compound of the invention.

Also the optional salification of a compound of the invention as well as the conversion of a salt into the free compound may be carried out by conventional methods.

The compounds of formula (II), (III), (V) and (VI) are known  
10 compounds or can be obtained by known methods.

When in the compounds of the present invention and in the intermediate-products thereof, groups are present, which need to be protected before submitting them to the hereabove illustrated reactions, they may be protected before being  
15 reacted and then deprotected according to methods well known in organic chemistry.

#### PHARMACOLOGY

The compounds of the invention are active on the central nervous system (CNS) and can be used in therapy, for example  
20 as antiepileptics, in the treatment of Parkinson's disease and as neuroprotective agents, e.g. preventing or treating neuronal loss associated with stroke, hypoxia, ischemia, CNS trauma, hypoglycaemia or surgery and in treating and  
25 preventing neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, Down's syndrome, Huntington's disease, dementia caused by acquired immunodeficiency syndrome (AIDS), infarctual dementia and infections or inflammations in the brain; they can also be  
30 used as antidepressants, hypnotics and antispastic agents and in treating ocular damage and retinopathy.

The activity on the CNS of the compounds of the invention was



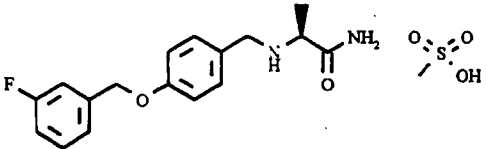
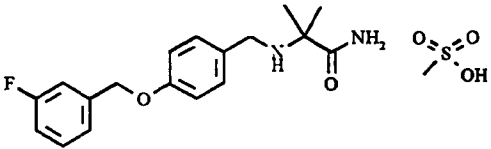
evaluated on the basis of pharmacological methods, such as, for example, the antagonism of convulsions and lethality induced by intravenous injection of bicuculline in mice (Antiepileptic Drugs, D.M. Woodbury et al. eds., 2nd edition, 5 Raven Press, New York, 1982), or the antagonism of maximal electroshock seizures (MES) (Woodbury, L.A. and Davenport, V.D., Arch. Int. Pharmacodyn. Ther. 92; 97-104, 1952).

The following table summarizes the activity data obtained by testing in the MES test a representative group of compounds 10 of the invention in comparison with the respective 2-desmethyl related compounds known from WO 90/14334.

The symbol \* identifies the prior art 2-desmethyl-compounds known from WO 90/14334.

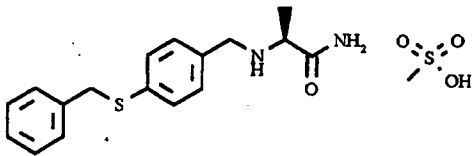
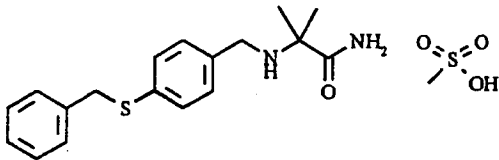
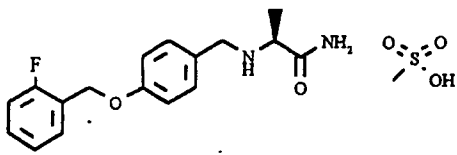
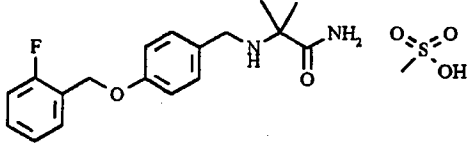
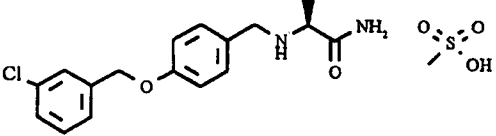
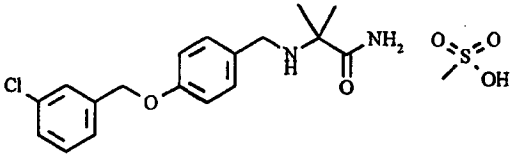
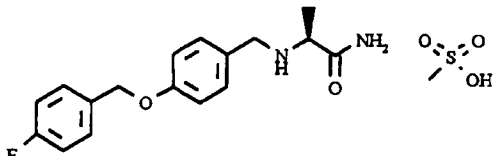
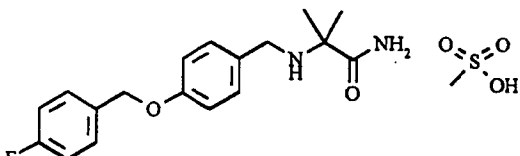
ED<sub>50</sub> means effective dose in 50% of treated animals after per 15 os (po) administration.

**Table 1**

Structure	Compound (internal code)	MES-ED <sub>50</sub> (po) mg/Kg
	FCE 26743A*	8.2 (7.2-9.4)
	FCE 29088A	4.4 (2.8-6.3)

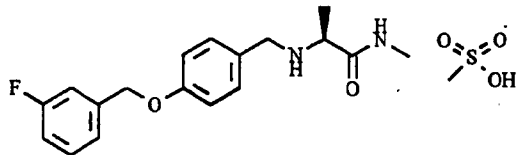
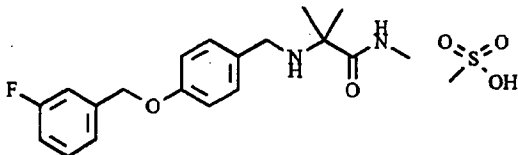
(cont..)

Table 1 (cont'd)

Structure	Compound (internal code)	MES-ED <sub>50</sub> (po) mg/Kg
	FCE 26727A*	12.72 (9.19-17.62)
	FCE 29482A	3.12 (2.28-4.27)
	FCE 26742A*	7.13 (5.70-8.91)
	FCE 29484A	3.10 (2.25-4.28)
	FCE 26193A*	9.41 (7.12-12.4)
	FCE 29644A	3.88 (2.90-5.19)
	FCE 26998A*	16.30 (7.18-37.12)
	FCE 29645A	6.58 (4.02-16.97)

(cont...)

Table 1 (cont'd)

Structure	Compound (internal code)	MES-ED <sub>50</sub> (po) mg/Kg
	FCE 28657A*	9.35 (4.34-13.11)
	FCE 29647A	4.34 (3.28-5.75)

where internal code:

- FCE 29088A means 2-(4-(3-fluorobenzoyloxy)benzylamino)-2-methyl-propanamide, methanesulfonate;
- 5 FCE 26743A\* means (S)-2-(4-(3-fluorobenzoyloxy)benzylamino)propanamide, methanesulfonate;
- FCE 29482A means 2-(4-benzylsulfanyl)benzylamino)-2-methyl-propanamide, methanesulfonate;
- 10 FCE 26727A\* means (S)-2-(4-benzylsulfanyl)benzylamino)propanamide, methanesulfonate;
- FCE 29484A means 2-(4-(2-fluorobenzoyloxy)benzylamino)-2-methyl-propanamide, methanesulfonate;
- FCE 26742A\* means (S)-2-(4-(2-fluorobenzoyloxy)benzylamino)propanamide, methanesulfonate;
- 15 FCE 29644A means 2-(4-(3-chlorobenzoyloxy)benzylamino)-2-methyl-propanamide, methanesulfonate;
- FCE 26193A\* means (S)-2-(4-(3-chlorobenzoyloxy)benzylamino)propanamide, methanesulfonate;
- 20 FCE 29645A means 2-(4-(4-fluorobenzoyloxy)benzylamino)-2-methyl-propanamide, methanesulfonate;
- FCE 26998A\* means (S)-2-(4-(4-fluorobenzoyloxy)benzylamino)propanamide, methanesulfonate;

FCE 29647A means 2-(4-(3-fluorobenzyloxy)benzylamino)-2-methyl-N-methylpropanamide, methanesulfonate;

FCE 28657A\* means (S)-2-(4-(3-fluorobenzyloxy)benzylamino)-N-methylpropanamide, methanesulfonate.

5

The comparative activity test data set out in the above table show that the new compounds of the instant invention are from 2 to 4 fold more active than the closely related prior art compounds.

10 A patient is treated according to the present invention by a method comprising administering to the patient an effective amount of one of the compounds of the invention. In this way the present compounds can be used to treat disorders of the central nervous system, for example epilepsy or Parkinson's  
15 disease; or as neuroprotective agents, anti-depressants, hypnotics or anti-spastic agents. The condition of a patient may thus be improved.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets,  
20 capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous injection or infusion.

The dosage depends on the age, weight, conditions of the  
25 patient and on the administration route; for example, the dosage adopted for oral administration to adult humans e.g. for the representative compound of the invention 2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-propanamide may range from about 1 to about 500 mg pro dose, from 1 to 5 times  
30 daily.

The invention includes pharmaceutical compositions comprising a compound of the invention, as an active principle, in

association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, destrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspension.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspension and the emulsion may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a

pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusion may contain  
5 as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa  
10 butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the invention.

15 Example 1

2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-propanamide,  
methanesulfonate (FCE 29088A)

To a solution of 2-amino-2-methylpropanamide, hydrochloride  
20 (7.01 g; 0.051 mol) in anhydrous methanol (160 ml), under stirring and nitrogen, 7.0 g of 3Å molecular sieves were added and then, in a single portion, NaBH<sub>3</sub>CN (2.31 g; 0.037 mol), after 10 minutes, 10.6 g (0.046 mol) of 4-(3-fluorobenzyloxy) benzaldehyde were added, in 140 ml of  
25 anhydrous methanol. After 24 hours the reaction was completed, the mixture filtered, the solution was evaporated to give a residue which was directly flash-chromatographed on silica gel (eluant: CHCl<sub>3</sub> 98: CH<sub>3</sub>OH 2: 30% NH<sub>4</sub>OH 0.15) to afford a white solid (6.2 g; 43%). The free base thus  
30 obtained was treated with a stoichiometric amount of methanesulfonic acid to yield the title compound (m.p. 209-213°C).

Analogously, the following products can be obtained, starting from the corresponding aldehyde and the appropriate amide:

- 2-[4-(3-chlorobenzyloxy)benzylamino]-2-methyl-propanamide,  
5 methanesulfonate, m.p. 202-206°C (FCE 29644A);
- 2-[4-(3-bromobenzyloxy)benzylamino]-2-methyl-propanamide,  
methanesulfonate, m.p. 197-202°C (FCE 29494A);
- 2-[4-(4-fluorobenzyloxy)benzylamino]-2-methyl-propanamide,  
methanesulfonate, m.p. 233°C (FCE 29645A);
- 10 2-[4-(2-fluorobenzyloxy)benzylamino]-2-methyl-propanamide,  
methanesulfonate, m.p. 215-220°C (FCE 29484A);
- 2-[4-(3-fluorobenzylamino)benzylamino]-2-methyl-propanamide,  
dihydrochloride, m.p. 165° ca. (dec.) (FCE 29822A);
- 2-[(4-benzylsulfanyl)benzylamino]-2-methyl-propanamide,  
15 methanesulfonate, m.p. 214-215°C (FCE 29482A);
- 2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-N-methyl-  
propanamide, methanesulfonate, m.p. 213-218°C (FCE 29647A);  
and
- 2-[4-(4-chlorobenzyloxy)benzylamino]-2-methyl-propanamide,  
20 m.p. 226-227°C (FCE 29485A).

### Example 2

2-[[4-(3-fluorobenzyloxy)benzyl]methylamino]-2-methyl-  
propanamide (FCE 29486)

25

One g. (0.00316 mol) of 2-[(4-(3-fluorobenzyloxy)benzylamino)-2-methyl-propanamide are dissolved in acetonitrile (50 ml) under a nitrogen stream. To this mixture, 3.16 ml (0.0389 mol) of 37% formaldehyde and 0.29 g  
30 (0.00460 mol) of sodium cyanoborohydride are added at room temperature. After 20 minutes, glacial acetic acid is dropped

- up to neutrality of the solution. The mixture is stirred for 40 minutes and evaporated to dryness. 40 ml of 2N KOH are added to the residue. After extracting with ethyl acetate, washing with N/2 KOH and then with water and brine, the organic layer is dried on Na<sub>2</sub>SO<sub>4</sub>, then filtered and evaporated to obtain a residue which is flash-chromatographed on silica gel (eluant: CHCl<sub>3</sub> 200: CH<sub>3</sub>OH 3: 30% NH<sub>4</sub>OH 0.2) to give 0.75 (72%) of a white solid (m.p. 121-123°C).
- 10 Analogously the following products can be prepared starting from the corresponding secondary amine:
- 2-{{[4-(3-chlorobenzyloxy)benzyl]methylamino}-2-methylpropanamide; and
- 2-{{[4-(3-bromobenzyloxy)benzyl]methylamino}-2-methylpropanamide.
- 15

### Example 3

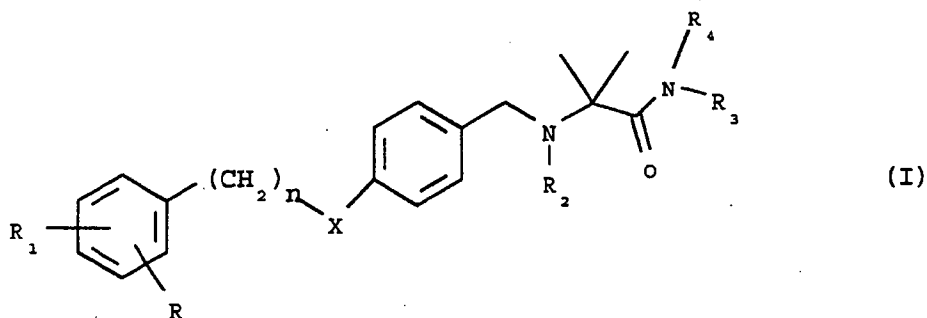
- With the usual methods of pharmaceutical technique, preparation can be made of capsules having the following composition:
- 20

2-[4-(3-fluorobenzyloxy)benzylamino]-2-methylpropanamide, methanesulfonate	50 mg
Talc	2 mg
Corn starch	2 mg
25 Microcristalline cellulose	6 mg
Magnesium stearate	1 mg



CLAIMS

1. A compound of formula (I)



5 wherein:

n is zero, 1, 2 or 3;

X is -O-, -S-, -CH<sub>2</sub>- or -NH-;

each of R and R<sub>1</sub> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy or trifluoromethyl;

10 each of R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>7</sub> cycloalkyl; or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I), according to claim 1,

15 wherein:

n is 1 or 2;

X is -O-, -S- or -NH-;

R is hydrogen;

R<sub>1</sub> is hydrogen or halogen;

20 each of R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> independently is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; or a pharmaceutically acceptable salt thereof.

3. A compound of formula (I), according to claim 1,

wherein:

25 n is 1;

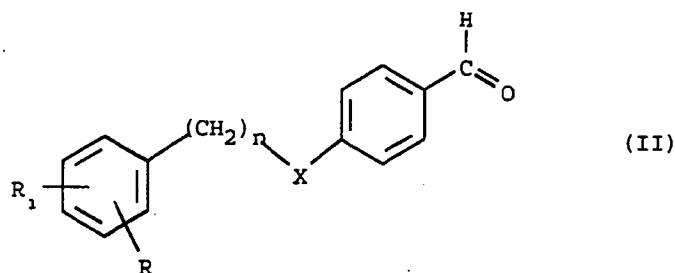
X is -O-, -S- or -NH-;

R<sub>1</sub> is hydrogen or halogen;

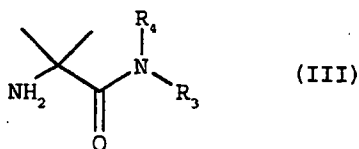
R, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are hydrogen; or a pharmaceutically acceptable salt thereof.

- 5        4. A compound selected from the group consisting of:
- 2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(3-chlorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(4-chlorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(3-bromobenzyloxy)benzylamino]-2-methyl-propanamide;
- 10 2-[4-(4-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(2-fluorobenzyloxy)benzylamino]-2-methyl-propanamide;
- 2-[4-(3-fluorobenzylamino)benzylamino]-2-methyl-propanamide;
- 2-[4-(benzylsulfanyl)benzylamino]-2-methyl-propanamide;
- 2-{[4-(3-fluorobenzyloxy)benzyl]-methylamino}-2-methyl-
- 15 propanamide;
- 2-[4-(3-fluorobenzyloxy)benzylamino]-2-methyl-N-methyl-
- propanamide;
- 2-{[4-(3-chlorobenzyloxy)benzyl]methylamino}-2-methyl-
- propanamide; and
- 20 2-{[4-(3-bromobenzyloxy)benzyl]methylamino}-2-methyl-
- propanamide, if the case, either as single (S) or (R) isomer
- or as a mixture thereof, or a pharmaceutically acceptable
- salt thereof.

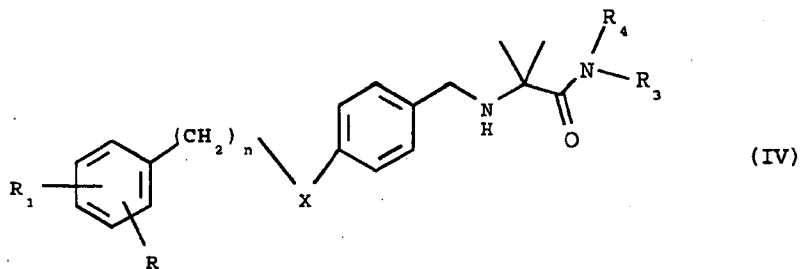
- 25        5. A process for the preparation of a compound of
- formula (I), as defined in claim 1, or a pharmaceutically
- acceptable salt thereof, the process comprising:
- a) reacting a compound of formula (II)



wherein  $n$ ,  $R$ ,  $R_1$  and  $X$  are as defined in claim 1, with a compound of formula (III)



- 5 wherein  $R_3$  and  $R_4$  are as defined in claim 1, thus obtaining a compound of formula (I) in which  $R_2$  is hydrogen; or  
 b) reacting a compound of formula (IV)



- wherein  $R$ ,  $R_1$ ,  $R_3$ ,  $R_4$ ,  $n$  and  $X$  are as defined in claim 1, with  
 10 a compound of formula (V) or (VI)



- wherein  $W$  is a halogen atom;  $R'_2$  is a  $C_1$ - $C_6$  alkyl and  $R''_2$  is hydrogen or  $C_1$ - $C_5$  alkyl, thus obtaining a compound of the invention in which  $R_2$  is  $C_1$ - $C_6$  alkyl; and, if desired,  
 15 converting a compound of the invention into another compound of the invention and/or, if desired, converting a compound of the invention into a pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound.

- 20 6. A pharmaceutical composition containing a suitable carrier and/or diluent and, as an active principle, a compound of

formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I), as defined in claim 1, or  
5 a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance.

8. A compound of formula (I), as defined in claim 1, or  
a pharmaceutically acceptable salt thereof, for use as  
10 antiepileptic agent, in the treatment of Parkinson's disease, as neuroprotective agent and in treating and preventing neurodegenerative diseases.

9. A compound of formula (I), as defined in claim 1, or  
15 a pharmaceutically acceptable salt thereof, for use in treating ocular damage and rethinopaty.

10. A compound of formula (I), as defined in claim 1, or  
a pharmaceutically acceptable salt thereof, for use as  
20 antidepressant, hypnotic antispastic agent.

# INTERNATIONAL SEARCH REPORT

national Application No  
PCT/EP 96/02961

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07C237/06 A61K31/16 C07C321/30

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 14334 A (ERBA CARLO SPA) 29 November 1990 cited in the application see page 21; claims ---	
A	WO 94 22809 A (ERBA FARMITALIA) 13 October 1994 see claims; examples ---	
A	WO 94 22808 A (ERBA FARMITALIA) 13 October 1994 see claims; examples -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

22 November 1996

Date of mailing of the international search report

29. 11. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

Sánchez García, J.M.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/02961

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9014334	29-11-90	AU-B- 645752	27-01-94
		AU-A- 5729990	18-12-90
		CA-A- 2033190	26-11-90
		CN-A,B 1047496	05-12-90
		CZ-A- 9002520	12-06-96
		DE-D- 69004337	09-12-93
		DE-T- 69004337	24-02-94
		EP-A- 0400495	05-12-90
		EP-A- 0426816	15-05-91
		ES-T- 2062174	16-12-94
		IE-B- 63934	28-06-95
		IL-A- 94466	24-01-95
		JP-T- 4500215	16-01-92
		NO-B- 179944	07-10-96
		US-A- 5391577	21-02-95
		US-A- 5502079	26-03-96
US-A- 5276611	04-01-94		
US-A- 5236957	17-08-93		
-----			
WO-A-9422809	13-10-94	AU-B- 667169	07-03-96
		AU-A- 6377694	24-10-94
		CA-A- 2136008	13-10-94
		CN-A- 1104018	21-06-95
		EP-A- 0648202	19-04-95
		FI-A- 945582	28-11-94
		HU-A- 70944	28-11-95
		JP-T- 8504828	28-05-96
		NZ-A- 263183	27-02-96
		PL-A- 306538	03-04-95
		US-A- 5449692	12-09-95
		ZA-A- 9401964	19-10-94
		-----	
WO-A-9422808	13-10-94	AU-B- 667164	07-03-96
		AU-A- 6284294	24-10-94
		CA-A- 2135783	13-10-94
		CN-A- 1104017	21-06-95
		EP-A- 0643688	22-03-95
		FI-A- 945581	28-11-94
		HU-A- 68256	28-06-95
		JP-T- 7507814	31-08-95

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/02961

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9422808		NZ-A- 262907	27-02-96
		PL-A- 306537	03-04-95
		US-A- 5446066	29-08-95
		ZA-A- 9401963	19-10-94
-----			